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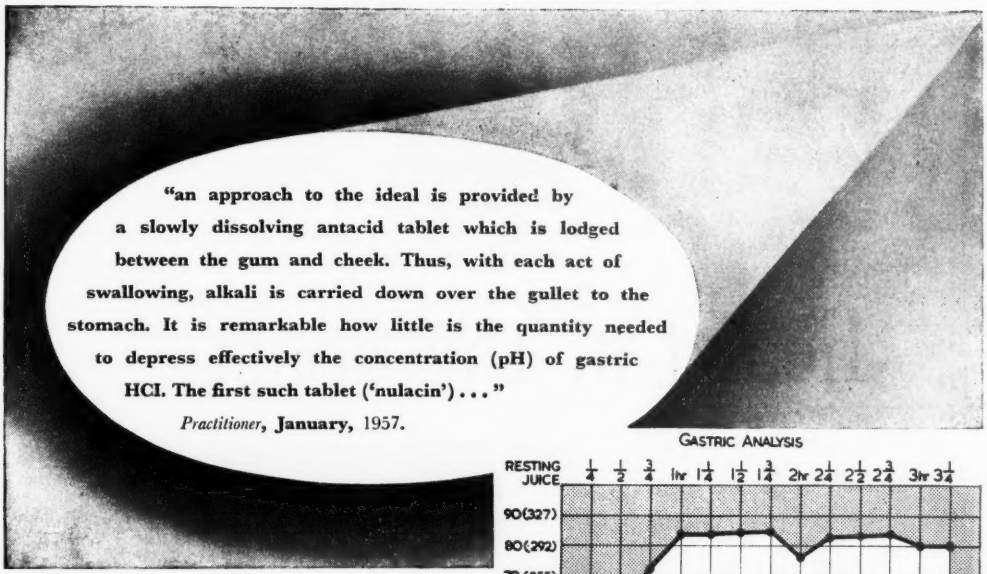

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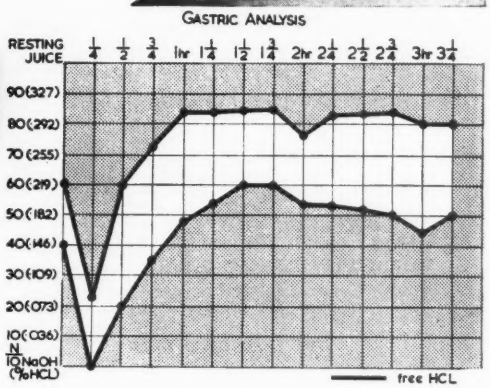

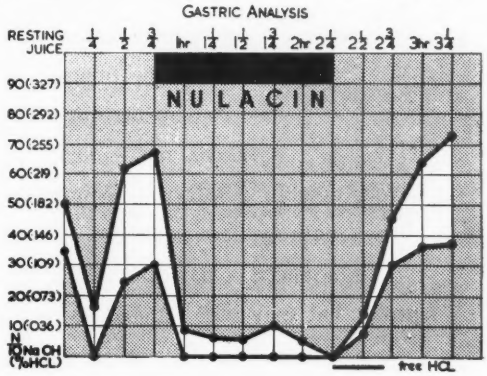

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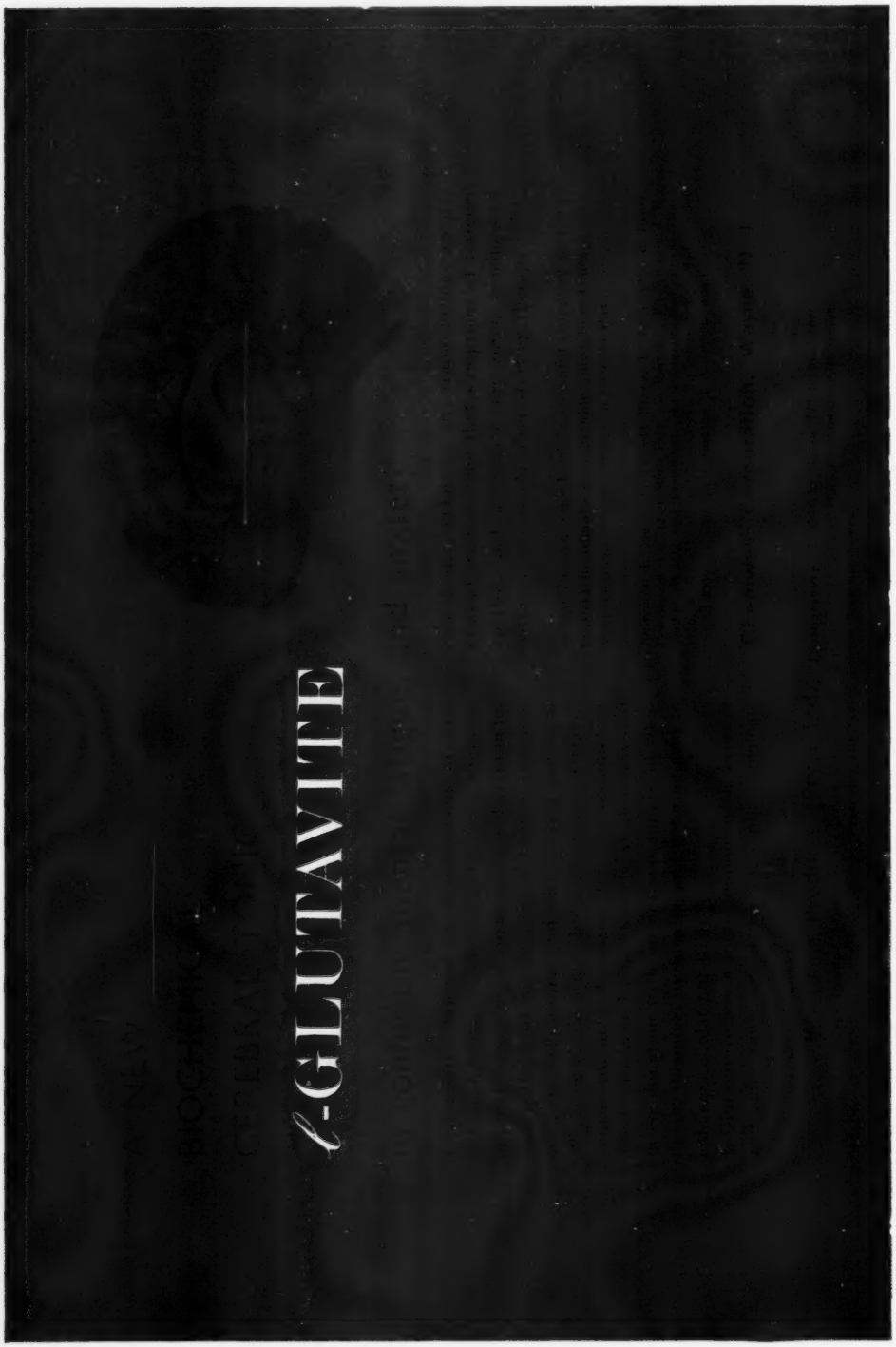
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P.O. Box 1010 · Johannesburg | Posbus 1010 · Johannesburg

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H. A. Shapiro, B.A., Ph.D., M.B., Ch.B., F.R.S.S.Af.

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REDAKSIONEEL · EDITORIAL

DIE ROOK VAN SIGARETTE AS OORSAAK VAN LONGKANKER

DIE EVOLUSIE VAN 'N FABEL?

Die geskil wat in die jongste tyd ontstaan het oor die rook van sigarette as 'n belangrike (of uiters belangrike) oorsaak van longkanker beklemtoon die noodsaaklikheid van 'n besonder deurtastende evaluasie van etiologiese aansprake as hulle op die dryfsand van statistieke gegrond is.

In 'n definitiewe bydrae wat elders in hierdie uitgawe gepubliseer word, sê dr. Berkson tereg:

‚Kanker is 'n biologiese en nie 'n statistiese probleem nie. By die toeligting daarvan sal statistieke miskien met reg 'n aanvullende rol kan speel. Maar as bioloë toelaat dat statistici die arbiters oor biologiese kwessies word, is 'n wetenskaplike ramp onvermydelik.'

Die soort bewyse wat op assosiasie staatmaak om 'n skuldigbevinding te verkry, is net so ongeldig in die wetenskaplike navorsingswêreld as wat dit in die politiek is, en is ewe laakbaar. Temeer, dit is hoogs twyfelagtig of statistieke ooit aangewend kan of behoort te word vir doeleindes wat vreemd aan hul eie besondere funksies is.

Soos ons reeds by 'n vorige geleentheid daarop gewys het by die bespreking van die lokvalle wat deur statistieke gestel word, is dit onvermydelik dat dinge wat oorsaaklik aan mekaar verbind is uit 'n statistiese oogpunt 'n hoë mate van korrelasie sal toon; maar 'n hoë mate van korrelasie tussen twee dinge wat bestudeer word, weerspieël nie noodwendig 'n oorsaaklike verband nie.[1]

Die dwaasheid van so 'n veronderstelling word op 'n sprekende wyse toegelig deur

1. Redaksioneel, 1956: Hierdie tydskrif, 21 Julie, bl. 341.

CIGARETTE SMOKING AS A CAUSE OF LUNG CANCER

THE EVOLUTION OF A MYTH?

The current controversy which has developed about smoking cigarettes as an important (or as a most important) cause of lung cancer, emphasizes the need for the most searching appraisal of claims about aetiology when they are based on the quicksands of statistics.

As Dr. Berkson points out in a definitive contribution published elsewhere in this issue:

'Cancer is a biologic, not a statistical, problem. Statistics can soundly play an ancillary role in its elucidation. But if biologists permit statisticians to become the arbiters of biologic questions, scientific disaster is inevitable.'

The kind of proof which relies on the smear of guilt by association has no greater validity in scientific research than it has in the field of politics; and it is just as objectionable. Moreover, it is extremely doubtful whether statistics could or should ever be perverted to uses foreign to its functions.

As we have previously pointed out when discussing the snares of statistics, things which are causally connected must show a high degree of correlation statistically; but a high degree of correlation between two things studied does not necessarily reflect a causal relationship between them.[1]

The fatuity of such an assumption is tellingly illustrated by Oschner's pertinent reminder that the increased incidence of bronchogenic carcinoma can be matched as easily by the increased sale of nylon stockings as by the increased sale of cigarettes; or by Rigdon and Kirchoff's observation that the 4%

1. Editorial (1956): This Journal, 21 July, p. 341.

Oschner se pertinente opmerking dat die toenemende voorkoms van bronchogeenkarsinoom ewe maklik in verband gebring kan word met die toenemende verkoop van nylonkouse as met die stygende afset van sigarette; of deur Rigdon en Kirchoff se waarneming dat die 4%-toename in huwelike in Arkansas in 1951 saamgeval het met 'n toename in die verkoop van haelgeweerkoeëls. Die jongste voorbeeld (wat moontlik swanger gaan aan Freudiaanse betekenis vir diegene wat psigo-analities aangelê is) kom van professor Udny Yule wat bevind het dat daar 'n groot aantal egskeidings in Groot-Brittanje was juis gedurende die jare toe daardie land 'n geweldige aantal appels ingevoer het.

'Die korrelasie was opvallend, statisties betekenisvol op 'n hoë peil van belang, en onmiskenbaar. Maar gelukkig het niemand tot die gevolgtrekking geraak dat die appels die egskeidings veroorsaak het of dat die egskeidings die rede vir die invoer van die appels was nie . . . korrelasie is nie veroorsaking nie.'[2]

Dr. Berkson se ontleding in hierdie uitgawe rig verdere verwoesting aan onder die bouvalle wat oorgebly het na sy vroeëre aanval op die voorstanders van die teorie dat die rook van sigarette 'n belangrike oorsaak van longkanker is. Hy toon aan dat daar 'n verband is met kankers behalwe longkanker, bv. kanker van die prostaat, die maag en die alvleesklier. Hy laat die soeklig op talle ander paradokse val, en kom tot die gevolgtrekking, in sy hoedanigheid as lid van 'n komitee wat verantwoordelik was vir die publikasie van sommige van die belangrikste studies wat op hierdie besondere navorsingsgebied onderneem is, dat die aansprake i.v.m. 'n oorsaaklike verband tussen die rookgewoonte en longkanker glad nie so gegrond of oortuigend is

'as wat skynbaar allerweë gemeen word nie. In die studies wat as „retrospektief" bestempel is, sowel as in dié wat „prospektief" genoem word, het ek betwyfelbare 'en selfs paradoksale elemente gevind.'

Dit skyn asof daar oortuigende bewyse is dat die voorkoms van longkanker 'n stygende neiging sedert die begin van die huidige eeu getoon het, maar die siekte het meer slagoffers onder mans as onder vrouens opgeëis. Sir Ronald Fisher noem dit[3]

'een van die massiewe en weerspannige feite wat te voorskyn getree het van agter die rookskerm van propaganda. . . . Die absolute toenamesyfer word natuurlik verduister deur verbeterde diagnostiese metodes, en deur die toenemende aandag wat aan hierdie siekte bestee word, maar die relatiewe proporsionele veranderings by mans en vrouens behoort vry van sodanige versteurings te wees, en die verandering was beslis tot nadeel van die mans.

2. Aangehaal deur sir Ronald Fisher in *Smoking: The Cancer Controversy*, 1959, bl. 14. Londen en Edinburgh: Oliver en Boyd.
3. *Op. cit.*, bl. 8–9.

increase in marriages in Arkansas in 1951 was also paralleled by an increase in the sale of shot-gun shells. The latest example (possibly fraught with Freudian significance for those with a psycho-analytical bent) has been produced by Professor Udny Yule, who found that in the years in which a large number of apples were imported into Great Britain there was also a large number of divorces.

'The correlation was large, statistically significant at a high level of significance, unmistakable. But no one, fortunately, drew the conclusion that the apples caused the divorces or that the divorces caused the apples to be imported . . . *correlation is not causation.*'[2]

Dr. Berkson's analysis in this issue further devastates the ruins which were left after his previous assaults on the protagonists of the theory that cigarette smoking is an important cause of lung cancer. He shows that there is an association with cancers other than lung cancer, including e.g. cancer of the prostate, the stomach and the pancreas. He highlights many other paradoxes and concludes, in his capacity as a member of a committee that has sponsored some of the most important studies published in connexion with research in this field, that the claims of a causal connexion between smoking and lung cancer are not so sound or convincing

'as they apparently have widely been assumed to be. In the studies that have been called "retrospective" as well as those called "prospective," I find questionable and even paradoxic elements.'

There seems to be persuasive evidence that the incidence of lung cancer has undoubtedly shown a marked upward trend since the turn of the century, but the disease has increased more rapidly in men than in women. Sir Ronald Fisher calls this[3]

'one of those massive and recalcitrant facts which have been emerging through the smoke-screen of propaganda. . . . The absolute rate of increase is, of course, obscured by improved methods of diagnosis, and by the increased attention paid to this disease, but the relative proportionate changes in men and women should be free from these disturbances, and the change has gone decidedly against the men. But it is notorious and conspicuous in the memory of most of us that over the last fifty years the increase in smoking among women has been great, and that among men (even if positive) certainly small. The theory that increased smoking is "the cause" of the change in apparent incidence of lung cancer is not even tenable in face of this contrast.'

Kirchoff and Rigdon[4] have examined the data on the sex incidence of lung cancer between 1856 and 1954. There is evidence

2. *Quoted* by Sir Ronald Fisher in *Smoking: The Cancer Controversy* (1959): p. 14. London and Edinburgh: Oliver and Boyd.
3. *Op. cit.*, pp. 8–9.
4. Kirchoff, H. and Rigdon, R. H. (1959): Texas Rep. Biol. Med., **17**, 29.

Maar dit is 'n berugte en opvallende feit wat aan die meeste van ons bekend is dat die toename van die rookgewoonte onder vrouens gedurende die afgelope vyftig jaar baie groot was, en dat dit (hoewel positief) slegs op 'n kleiner skaal onder mans toegeneem het. In die lig van hierdie teenstelling is die teorie dat die toenemende rookgewoonte „die oorsaak" is van die verandering in die skynbare voorkoms van longkanker, nie eens verdedigbaar nie.'

Kirchoff en Rigdon[4] het ondersoek ingestel na gegewens oor die voorkoms van longkanker by mans en vrouens gedurende die tydperk 1856 tot 1954. Daar is bewyse dat longkanker gedurende hierdie tydperk in 'n groter mate by mans as by vrouens toegeneem het (die verhouding was 3:1 of 4:1 in 1900 in vergelyking met 5:1 of 6:1 in 1955).

Inderdaad is daar 'n hele reeks van ‚massiewe en weerspannige feite' wat dit onmoontlik maak om die suggestie dat die rookgewoonte 'n betekenisvolle oorsaak van longkanker is, as 'n praktiese voorstel te aanvaar. Hieronder verstrek ons dan ook 'n lys van hierdie feite:

1. Eastcott se studie van die epidemiologie van longkanker in Nieu-Seeland[5] het aangedui dat daar meer gevalle van longkanker onder immigrante uit Groot-Brittanje voorkom as onder Nieu-Seelanders, en dat daar 'n verband met vroeëre verstedeliking was. Die verbruik van tabak per kop van die bevolking in Nieu-Seeland stem egter met die verbruik in Groot-Brittanje ooreen, maar die longkankersyfer in eersgenoemde land is net die helfte so groot as in laasgenoemde. Die sterftesyfer ten gevolge van longkanker was hoër onder immigrante uit Engeland as onder persone wat in Nieu-Seeland gebore is.

Ons het reeds by 'n vorige geleentheid gewys op 'n teenstrydigheid in die gegewens vir Australië, soortgelyk aan die toestand wat nou deur Eastcott in Nieu-Seeland aan die lig gebring is. Gedurende die tydperk van die studie was die tabakverbruik in Australië omtrent net so groot soos dié in die Verenigde Koninkryk. En tog het longkanker die lewe van net 'n kwart soveel Australiërs opgeëis as in die ooreenstemmende ouderdomsgroepe in die Verenigde Koninkryk.[6]

2. Die oorspronklike studies deur Doll en Hill waarop die hele hipotese gegrond is, het aangedui dat die aantal gevalle van longkanker in die plattelandse streke betekenisvol kleiner is as die aantal gevalle onder stedelike bevolkings. Op grondslag van die rook van sigarette is geen bevredigende verduideliking vir hierdie verskil aan die hand gedoen nie. Trouens, daar is bewys dat die stedeling, betreklikerwyse gesproke, net effens meer as die platte-

4. Kirchoff, H. en Rigdon, R. H. (1959): Texas Rep. Biol. Med., **17**, 29.
5. Eastcott, D. F. (1956): Lancet, **1**, 37.
6. Redaksioneel (1956): Hierdie tydskrif, 21 Julie, bl. 343.

that during this time the increase in lung cancer has been greater in the male than in the female (the ratio being about 3:1 or 4:1 in 1900 and 5:1 or 6:1 in 1955).

Indeed there is a whole series of 'massive and recalcitrant facts' which make it impossible to accept as feasible the suggestion that cigarette smoking is a cause of lung cancer of any significance. We list a few of them:

1. Eastcott's study of the epidemiology of lung cancer in New Zealand[5] indicated that immigrants from Great Britain had a higher incidence of lung cancer than New Zealanders and that the association was with previous urbanization. Tobacco consumption per head of population in New Zealand, however, was similar to that in Great Britain, but the lung cancer rate was only half. The death rate from lung cancer was higher in the immigrants from England than in the native-born New Zealanders.

We have previously pointed out a disparity in the data for Australia similar to the situation uncovered by Eastcott in New Zealand. In Australia the tobacco consumption per head for the period studied was about the same as in the United Kingdom. Yet the lung cancer incidence amongst Australians was about a quarter of that in corresponding age groups in the United Kingdom.[6]

2. The original studies by Doll and Hill, on which the whole hypothesis is based, recorded a significantly lower incidence of lung cancer in rural as opposed to urban populations. No satisfactory explanation was forthcoming for this discrepancy on the basis of cigarette smoking. Indeed, there is evidence that men living in cities smoke relatively little more than men living in rural areas. There is a greater difference between town and country in the smoking habits of women.

3. Non-ferrous male workers and transportation employees have the highest incidence of lung cancer and farm labourers the lowest.

4. Women in similar occupations have lung cancer rates comparable to those of men.

5. Male industrial life insurance policy holders engaged in manufacturing, mining and transportation and who come from low income groups, have lung cancer rates of 30-50% higher than general policy holders who are engaged in office work.

6. If the latent period for lung cancer development is 20 years, the death rate should have been higher during 1931–1944 than the annual progression rates were for deaths in

5. Eastcott, D. F. (1956): Lancet, **1**, 37.
6. Editorial (1956): This Journal, 21 July, p. 343.

lander rook. Daar is 'n groter verskil tussen die rookgewoontes van vroue in die stede en vroue op die platteland.

3. Die grootste aantal gevalle van longkanker kom voor onder mans wat in die nie-ysterbedrywe en in die vervoerbedryf werksaam is, en die kleinste aantal onder plaasarbeiders.

4. Die longkankersyfers vir vrouens wat dergelike beroepe volg, kan met die syfers vir mans vergelyk word.

5. Die longkankersyfer is van 30–50% hoër by mans wat industriële lewensversekeringspolisse uitgeneem het, by die vervaardigings-, myn- en vervoerbedrywe betrokke is, en onder die lae-inkomstegroep ressorteer as by algemene polishouers wat kantoorwerk doen.

6. Indien die latente tydperk vir die ontwikkeling van longkanker 20 jaar is, behoort die sterftesyfer gedurende die tydperk 1931–1944 hoër te gewees het as die jaarlikse progressiewe syfers vir sterfgevalle in die Verenigde State gedurende 1914–1930, uitgaande van die veronderstelling dat die rook van sigarette 'n belangrike faktor is.[9]

7. Rigdon en Kirchoff[7] het aangetoon dat hoewel die aantal sigarette wat per persoon in New York en Idaho verkoop word, min of meer eners is, die sterftesyfer ten gevolge van longkanker 4 keer hoër in New York is.

Die Verenigde Koninkryk waar die voorkoms van longkanker ontstellend hoog is, neem derde plek in onder die 22 lande alwaar die verkoop van sigarette in pakkies ondersoek is. Die V.S.A. beklee tweede plek, en die blanke bevolking van Suid-Afrika staan bo aan die lys. Op grondslag van die totale verbruik van alle soorte tabak per kop van die bevolking neem die Verenigde Koninkryk 9de plek onder 22 lande in.

'n Vergelykende studie van die posisie in verskillende dele van die wêreld dui aan dat die aanspraak dat die rook van sigarette die oorsaak van longkanker is, met die grootste skeptisisme bejeën moet word. Die omgewingsoorsake van longkanker vereis heel duidelik nougesetter aandag en doeltreffender evaluasie. Atmosferiese besmetters (met bekende karsinogeniese eienskappe) wat met nywerheidsontwikkeling en die meganisasie van vervoer in verband staan, speel miskien 'n baie belangriker rol as wat ons besef of vermoed. Hierdie verontreinigers kom voor in die lug wat deur stedelike bevolkings ingeasem word. Dit skep 'n toestand wat in skerp teenstelling staan met die proefnemings met *velkanker* wat uitgevoer is deur die afgeskeerde *velle* van muise te bestryk met teeruittreksels afkomstig van tabakrook in 'n konsentrasie wat geen verband hou met wat in die asemhalingskanaal gebeur selfs wanneer 'n mens die rook inasem nie. Die resultate van die proefnemings met ‚rokende' muise wat deur die ‚British Empire Cancer Campaign' onderneem is, het die uitvoerige hipotese wat deur die verkondigers van die kwaadaardige euwels van die rookgewoonte opgebou is, in elk geval volkome weerlê.

8. Ons het reeds by 'n vorige geleentheid[8] die aandag gevestig op die hoogs belangrike anomalie dat die inaseming van sigaretrook nie in verband met die voortbrenging van longkanker gebring kan word nie, veral aangesien daar beweer word dat die gevaar dat 'n mens aan longkanker sal sterf in regstreekse verhouding staan tot die hoeveelheid tabak wat jy rook.

7. Rigdon, R. H. en Kirchoff, C. H. (1952): Texas Rep. Biol. Med., **10,** 76.
8. Redaksioneel (1956): Hierdie tydskrif, 21 Julie, bl. 344.
9. Hueper, W. C. (1956): Pub. Hlth. Rep., **71,** 94.

the United States during 1914–1930 on the assumption that cigarette smoking is an important factor.[9]

7. Rigdon and Kirchoff[7] have shown that although the number of cigarettes sold per person was about the same in New York and Idaho, the lung cancer death rate was 4 times higher in New York.

The United Kingdom with its alarmingly high incidence of lung cancer, is third of 22 countries surveyed for consumption of packeted cigarettes. The U.S.A. ranks second and the White population of South Africa is in the first place. On the basis of total consumption per head of all forms of tobacco, the United Kingdom ranks 9th of 22 countries.

The comparative studies of the position in different parts of the world indicate the need to challenge with the greatest scepticism the claim alleging that smoking cigarettes causes lung cancer. The environmental causes of lung cancer clearly require more adequate attention and evaluation. Atmospheric pollutants (with known carcinogenic properties) related to industrial development and mechanization of transport may be very much more important than was realized or suspected. These pollutants occur in the air which the urban population breathes. This provides a situation in striking contrast to the experiments on *skin* cancer conducted with extracts of tar from tobacco smoke, painted on to the shaved *skins* of mice, in a concentration which bears no relation to what happens in his respiratory tract, even when a smoker inhales. In any event, the results of the British Empire Cancer Campaign's experiments with 'smoking' mice have completely negatived the elaborate hypothesis constructed by the proponents of the malignant evils of smoking.

8. We have previously drawn attention[8] to the crucial anomaly that inhalation of cigarette smoke was unrelated to the production of lung cancer, especially as it has been claimed that the risk of dying from lung cancer is directly proportional to the amount smoked. The investigation of carcinogens in tobacco smoke rests on the theory that when they are inhaled they will provide the development of lung cancer. In view of this assumption, it is an inevitable inference that the incidence of the disease should be greater in inhalers than in non-inhalers. The striking failure to substantiate this point factually constitutes a fatal con-

7. Rigdon, R. H. and Kirchoff, C. H. (1952): Texas Rep. Biol. Med., **10,** 76.
8. Editorial (1956): This Journal, 21 July, p. 344.
9. Hueper, W. C. (1956): Pub. Hlth. Rep., **71,** 94.

Die ondersoek van karsinogene in tabakrook berus op die teorie dat hulle die ontwikkeling van longkanker bevorder as hulle ingeasem word. Uitgaande van hierdie veronderstelling moet ons tot die onvermydelike gevolgtrekking geraak dat die voorkoms van die siekte groter onder inasemers as onder nieinasemers behoort te wees. Die opvallende mislukking om hierdie punt feitelik te bewys is 'n vernietigende weerspreking van die hipotese wat postuleer dat die rookgewoonte 'n oorsaak van longkanker is.

Die feite in verband met die inaseming van tabakrook is skynbaar so onaangenaam vir die luidrugtige voorstanders van die genoemde hipotese dat dit amper wil voorkom asof hierdie feite met groot vlytigheid onderdruk word. Sir Ronald Fisher het nou inderdaad 'n baie skerp lig laat val op hierdie buitengewone poging om partydige propaganda te maak deur 'n baie lastige en weerspannige feit te verswyg. Die posisie wat deur sir Ronald Fisher aangetoon en gegrond is op 'n rekonstruksie van die oorspronklike waarnemings van Doll en Hill is in werklikheid dat minder gevalle van longkanker by rook-inasemers voorkom, en dat die verskil statisties betekenisvol is. Soos sir Ronald Fisher dit stel: [3]

,Behoort hierdie werkers die wêreld nie in kennis te gestel het nie alleen dat hulle die oorsaak van longkanker (sigarette) gevind het nie, maar ook dat hulle die voorbehoedmiddel (die inaseming van die rook) ontdek het? Hoe het die M.R.C. dit oor sy hart gekry om hierdie inligting te weerhou van die duisendes wat daarsonder aan longkanker gaan sterf?

Diegene wat weier om die sprong vanaf assosiasie tot by oorsaak te doen in die geval van die rook van sigarette, sal nie verlei word om dit te waag in die geval van die inaseming van sigaretrook nie, maar die M.R.C. en sy Statistiese Navorsingseenheid meen dat die argument geldig is in die eerste geval. Kan hulle weier om dit aan te neem in die tweede?' (bl. 47).

Daar bly dus 'n werklike behoefte om deurtastende ondersoek in te stel na die oorsake van longkanker, maar dit is ook ons plig om hierdie navorsingswerk voort te sit sonder seepkis-redenasies op die markplein, of die hoë-druk-tegniek van propaganda wat beter by die verkoopsagent as by die wetenskaplike pas. Daar is geen bewyse wat as regverdiging kan dien vir verbodveldtogte, gekleur deur 'n emosionele houding wat heeltemal vreemd aan besadigde ondersoekmetodes is nie.

Voorbarige gevolgtrekkings wat deur die meeste wetenskaplikes nie as oortuigend en dringend genoeg beskou word nie, kan ons inderdaad laat afdwaal van die pad wat ons na die regte oplossing kan lei. Die geld wat tans bestee word aan die navorsing van filters en die bepleiting van veranderings in die keuse en droogmaak van tabak kan, byvoorbeeld 'n ongeoorloofde en tevergeefse verkwisting van tyd en geld wees op 'n skaal wat sonder weerga in die geskiedenis van mediese navorsing is. Die beweerde geneesmiddels is gebaseer op 'n veronderstelling wat klaarblyklik nie waar is nie. Miskien is ons besig om die evolusie van 'n fabel te aanskou.

Dit is ook nodig dat ons ons moet losmaak van die pogings om geld van die tabakbedryf af te pers vir die subsidiëring van heeltemal ongeoorloofde navorsingskemas. Sodanige pogings word in die buiteland aangewend met al die lawaaierigheid van 'n trop honde wat 'n haas agternasit, en eggo's van hul geblaf is selfs hier in Suid-Afrika gehoor. Ons vertrou van harte dat hoegenaamd geen gehoor aan hierdie onbehoorlike eise gegee sal word nie.

tradiction to the hypothesis which postulates smoking as a cause of lung cancer.

The facts about inhaling were apparently so unpalatable to the vociferous protagonists of this view, that they appear to have been most sedulously suppressed. Indeed, Sir Ronald Fisher has now fully exposed this extraordinary attempt to give a bias to propaganda by evading a very awkward and very recalcitrant fact. The position demonstrated by Sir Ronald Fisher (and based on a reconstruction of the original observations made by Doll and Hill) is that inhalers get fewer lung cancers and that the difference is statistically significant. As Sir Ronald Fisher says: [3]

'Should not these workers have let the world know not only that they had discovered the cause of lung cancer (cigarettes), but also that they had discovered the means of its prevention (inhaling cigarette smoke)? How had the M.R.C. the heart to withhold this information from the thousands who would otherwise die of lung cancer?

Those who refuse to jump from association to causation in the case of cigarette smoking will not be tempted to take it in the case of inhaling; but the M.R.C. and its Statistical Research Unit think the argument is valid in the first case. Can they refuse to admit it in the second?' (p. 47).

There remains a real need to concern ourselves with the causes of lung cancer, but we have a duty to pursue this research without the tub-thumping of the market place or high pressure techniques of propaganda more appropriate to the salesman than the scientist. There is no evidence which justifies us in embarking upon the campaigns of prohibition which are coloured by an emotional attitude wholly foreign to dispassionate methods of investigation.

Premature conclusions based on data which the general body of men of science do not find sufficiently cogent and compelling, may even distract us from following the paths that could lead to the correct answer. The expenditure on research into filters and the advocacy of radical changes in the selection and curing of cigarette tobaccos may, for example, well become an unwarranted and misdirected effort (wasteful in time and money) on a scale unparalleled in the history of medical research. These are purported remedies based on premises not proved to be true. We may be witnessing the creation of a myth before our eyes.

There is also need to dissociate ourselves from attempts to blackmail the tobacco industry into subsidizing quite unsupportable research projects. These attempts have been made overseas with the stridency of hounds in full bay and a little echoing yelp has even been heard in South Africa. This quite improper demand will, it is to be hoped, fall on deaf ears.

SMOKING AND LUNG CANCER

SOME OBSERVATIONS ON TWO RECENT REPORTS*†

JOSEPH BERKSON, M.D.
Mayo Clinic, Rochester, Minnesota, U.S.A.

'I do not reject the use of statistics, but I condemn not trying to go beyond them . .'. *Claude Bernard.*

The opinion that smoking is a cause of cancer of the lung, expressed by a number of writers and reflected in some recent public announcements,[4, 16] rests to a considerable degree, though not entirely, on two now celebrated 'prospective' statistical studies, one reported by Doll and Hill,[5, 6] the other by Hammond and Horn.[10, 11] In a commentary article in 1955,[1] I pointed out that the results presented in the first report of Hammond and Horn[11] exhibited an association of smoking with increased death rates, not only for cancer of the lung, but also for each of the other several categories of cause of death into which all causes had been segregated, namely, cancer exclusive of lung, diseases of the coronary arteries, and other diseases. In the second report of these authors, the association of smoking with the death rates from causes other than lung cancer is shown even more clearly. In Fig. 4, which is reproduced from their recent report,[10] it is seen that, of the total estimated excess deaths attributed to regular cigarette smoking, only 13.5% were from lung cancer. Disease of the coronary arteries accounted for about 52% of the excess deaths, cancer other than lung cancer for 13.5%, other heart and circulatory disease for 5.8%, non-cancerous pulmonary disease for 5.6%, cerebral vascular disease for 4.8%, peptic ulcer for 2.8%, and cirrhosis of the liver for 1.5%.

When I wrote my article, only the first report of the prospective study of Doll and Hill had been published, and in their results, based on rather few deaths, a similar generalized association of smoking with death rates from causes other than cancer of the lung was not evident. In their second report, based on a longer follow-up, and consequently on more reported deaths, a generalized association similar to that found in the study of Hammond and Horn can be seen.

If what we wish to observe, when it is present, is evidence that smoking increases the probability of death from this or that disease, a simple and effective procedure, commonly used, is to examine an extreme, for instance in this case, the experience of the heavy smokers. It is reasonable to say:

'If smoking increases the risk of death, it should affect heavy smokers most; the first thing to do is to see whether the death rates of the heavy smokers are higher than the rates of those who are less than heavy smokers.'

One would not limit oneself to this comparison, of course, for a complete analysis of the character of the association, but for the particular purpose of discerning whether association does exist, this suggests itself as a sensitive method. In Table 29, the death rate of heavy smokers (25+ gm. daily average) is compared, for each of 5 categories of cause of death listed by Doll and Hill[5] in their Table V, with the death rate of non-smokers, that of light smokers (1–14 gm. daily average), and that of moderate smokers (15–24 gm. daily average).

It is to be noted that the heavy smokers have a higher death rate than the non-smokers for each category of cause of death listed, and that the difference in death rate is largest, not for lung cancer, but for coronary thrombosis. Comparing the death rate of the heavy smokers with that of the light smokers, again we find that the death rate is higher for the heavy smokers with each category of cause of death, and that the difference in death rate is largest, not for lung cancer, but for coronary thrombosis. And comparing the death rate of the heavy smokers with that of the moderate smokers, we find that the rate is higher for the heavy smokers with each cause of death, and that the difference is largest, not for lung cancer, but for coronary thrombosis, while the next largest difference is not for cancer of the

* Since publication of this article, the investigation of Hammond and Horn referred to in the text has been published in definitive form, and the reader may wish to refer to this (J. Amer. Med. Assoc., **166**, No. 10 and 11, 1958).

† Reprinted by permission of the author and the *Section on Publications* of the Mayo Clinic and the Editor of the *Journal of the American Statistical Association*, (March 1958).

lung either, but for cancer other than lung cancer. Even as the death rate among the heavy smokers is highest in each of the 5 categories of causes of death, so it is true also, that for all the categories except cancer other than lung cancer, the death rate is smallest among the non-smokers.

Doll and Hill measured the differences in death rates among the different classes of smokers relatively, sometimes in relation to the death rate among all men, sometimes in relation to the death rate among non-smokers. It seems almost instinctive to express differences relatively in some such manner, but in a case like the present application, it may be misleading. There are, of course, situations in which such relative measures are appropriate, but it does not appear to me that this is such a situation. When there is reason to believe that an increment δy, by the mechanism which produces it, is proportional to y, then we will measure the force producing δy in proportion to $\delta y/y$. In the present case δy is the increased number of deaths associated with smoking (in a standard number of the population, in a year), and we must consider whether y can be the total number of deaths, or the number not attributed to smoking. Smoking, when increasing deaths, if it has such an effect, produces this effect, in the first instance, by acting on the living; why, then, should its potency be measured in relation to the number of deaths? Indeed, conceivably, it might work the other way around. If, for instance, heart disease, independently of smoking, causes a greater number of deaths than lung cancer does, then smoking would have fewer susceptibles to kill with heart disease than with cancer of the lung. In that case, a given number of deaths from heart disease, attributed to smoking, would reflect a greater mortal force for heart disease than the same number of deaths would reflect for cancer of the lung. I have not been able to think of a reasonable theory of the action of smoking in causing death, for which it would be appropriate to measure the increased death rate from a specified disease, attributed to smoking, as a proportion of the total death rate from that cause. The exclusive use of this index, in the present instance, is open to criticism in particular, because it tends to bolster up the theory being advanced—the association of smoking and lung cancer—and to tone down the association with other causes of death. For instance, the death rate for lung cancer is about a sixth that for coronary thrombosis. Therefore, when measured relatively, a given number of deaths from lung cancer appears 6 times as large as the same number of deaths from coronary thrombosis. And, of course, from a strictly practical viewpoint, it is only the total number of increased deaths that matters. In the considerable literature that has developed about smoking and lung cancer, it is not the enormous import for biology of a discovery that smoking can

TABLE 29: DEATH RATES OF HEAVY SMOKERS COMPARED WITH THOSE OF LESS THAN HEAVY SMOKERS

	All Causes	*Lung Cancer*	*Other Cancer*	*Other Respiratory Diseases*	*Coronary Thrombosis*	*Other Causes*
Standardized death rate per year per 1,000 males*						
Non-smokers	13·25	0·07	2·04	0·81	4·22	6·11
Daily average of 1–14 gm.	14·92	0·47	2·01	1·00	4·64	6·82
Daily average of 15–24 gm.	14·49	0·86	1·56	1·11	4·60	6·38
Daily average of 25 + gm.	18·84	1·66	2·63	1·41	5·99	7·19
Difference, rate of heavy smokers and rate of:						
Non-smokers	5·59	1·59	0·59	0·60	1·77	1·08
Daily average of 1–14 gm.	3·92	1·19	0·62	0·41	1·35	0·37
Daily average of 15–24 gm.	4·35	0·80	1·07	0·30	1·39	0·81
Mean difference	4·62	1·19	0·75	0·43	1·50	0·75
Difference of rate, per cent of all causes						
Non-smokers	100·0	28·4	10·6	10·7	31·7	19·3
Daily average of 1–14 gm.	100·0	30·4	15·8	10·5	34·4	9·4
Daily average of 15–24 gm.	100·0	18·4	24·6	6·9	32·0	18·6
Mean difference	100·0	25·7	16·2	9·3	32·5	16·2

* From table V of Doll and Hill.[5] The death rate from all causes is less than the sum of the rates for the specific causes because of the inclusion of 3 cases of lung cancer in 2 categories of causes.

cause cancer that has been emphasized—hardly a word about that. Instead there has been great advertisement of the social evil causing so many people to die—and something should be done about that.* In these circumstances, it is especially to the point, that the *number* of deaths should not have been obscured, in a preoccupation with the *ratio* of deaths.

Thus, on the basis of a comparison of the death rates of heavy smokers with those who are less than heavy smokers, it is clearly indicated in these data that smoking, or at least heavy smoking, increases the probability of death from every cause, so far as these causes are represented in the 5 categories listed by Doll and Hill. If the mean of the differences of death rates between heavy smokers and less than heavy smokers is taken as an index, the difference of death rate from all causes is 4.6 (Table 29). Of this difference, the difference of death rate for coronary thrombosis constitutes 32%, while the difference in death rate for cancer of the lung constitutes only 26%. But none of the other categorized causes of death fails to contribute to the difference of rate from all causes; other cancers than lung cancer contribute 16%, other respiratory diseases 9%, and 'other causes' 16%. Doll and Hill emphasize in their discussion that, due to the attenuation of the data, any relation found 'will be an *understatement* of the true relationship,' and this seems to be a sound inference. Accordingly, the associations described above between smoking and each of the categorized causes of death can be considered an understatement of the true association between smoking and the death rate from causes represented in each of these categories.

Are these associations 'statistically significant'? We are not concerned, at the moment, with whether there is association with some specified category of disease, but with the validity of the evidence that there is association with disease in general. Appropriate here is some form of permutation test of the kind being developed by Box and Andersen.[2] However it is figured, the probability of getting by chance, if there were no generalized association with all or many of the separate categories of disease, consistently higher death rates among the heavy smokers than among any of the 3 categories of less than heavy smokers, in each of 5 pre-designated categories of cause of death, and in agreement with the independently obtained similar finding in the prospective study of Hammond and Horn, must be considered negligible. The appearance of a generalized association in the first report of Hammond and Horn, not clearly evident in the first report of Doll and Hill, is reasonably ascribable to the larger number of cases in the former study.† As already noted, with more death notices available in the second report of Doll and Hill, an association of smoking in all 5 categories of cause of death became discernible. When Doll and Hill present later reports, based on more ample data, such associations may be exhibited with even greater clarity.

The existence in the data of both these prospective studies, of association between smoking and death rate from many categories of cause of death other than lung cancer, and indeed chiefly with these other categories, raises a serious challenge to the explanation that the statistical association observed between smoking and lung cancer has a direct causal basis.‡ Some physical explanation must be found for the other associations, unless statistics is to be exposed to the charge of scientific

* What is to be done, it appears, is to be limited to hortatory efforts at dissuading people from smoking cigarettes. No programme has been initiated, for instance, to develop an immunizing vaccine, a step that, since Pasteur, has typically followed the identification of a specific cause of a disease.

† The total number of men in the study of Hammond and Horn was about 188,000; the number in the study of Doll and Hill was about 35,000. In the 53 months covered by the study of Doll and Hill[5] there were 1,714 deaths or 388 deaths per annum. In the 20 months experience of the report of Hammond and Horn[11] there were 4,854 deaths or 2,912 deaths per annum, relatively over 7 times as many. Considering the much greater numerical definitiveness of the study of the American Cancer Society, it is regrettable that it has been decided to terminate that study with its second report. In follow-up studies of this kind, it is frequently the late results which are the most revealing.

‡ In any critical analysis of statistics claiming to establish a causative association between disease and an environmental factor, the great importance of the *disease specificity* has rightly been stressed by Yerushalmy and Hilleboe.[17] The report of the Medical Research Council of England[13a] on cancer of the lung, seems, in part, to recognize this, when it says, referring to the retrospective investigation of Doll and Hill[6] 'Analysis of the histories and habits of the patients with various diseases revealed *only one* striking contrast—the difference in the smoking habits of those with and those without *lung cancer* (italics inserted).' Yet the report later refers to the study of Hammond and Horn,[11] in which the association with smoking, so far from being specific for lung cancer, is evident for each of the disease groups categorized; but the report makes no note of the fact.

irresponsibility.* It would assist materially in understanding the analysis of Doll and Hill, and that of Hammond and Horn, if we had answers, as clear and unequivocal as the complexity of the problem permits, to the following questions:

1. Is their explanation of the association of smoking with lung cancer, at least for a large proportion of the estimated excess deaths among smokers from this cause, about as follows? Cigarette smoke contains carcinogenic substances that, by contact with the bronchial and pulmonary tissues over a sufficiently long time, induce changes resulting in cancer.

2. Is their explanation for the association shown with cancers other than lung cancer, including cancer of such sites as the prostate, stomach and pancreas, also that the relation is causal? If so, what in general terms, is the mechanism of this causation?

3. Do they think that the association with the death rate from coronary heart disease, which has the largest number of estimated excess deaths associated with smoking or heavy smoking of any disease category, is causal? If not, what is their explanation of the association?

4. Do they have any explanation of the association of smoking with the death rate for the miscellaneous category of diseases, which excludes cancer, and cardiovascular disease and non-cancerous respiratory disease?

For myself, I find it quite incredible that smoking should cause all these diseases. It appears to me that some other explanation must be formulated for the multiple statistical associations found with so wide a variety of categories of disease. And if we are not crassly to violate the principle of Occam's razor, we should not attribute to each separate association a radically different explanation.

One explanation is that the associations have a constitutional basis. This hypothesis has been formulated—and rejected—by Doll and Hill[5] in the following terms:

'... it has been suggested that constitutional and psychological factors might have such an effect... that persons of a certain "make up" are peculiarly liable to lung cancer and to smoke. We know of no published evidence to this effect.' **

The hypothesis is stated more plausibly, it seems to me, to the effect that persons who are non-smokers, or relatively light smokers, are of a constitutional type that is biologically disposed to self-protective habits, and that this is correlated generally with constitutional resistance to mortal forces from disease. If 85 to 95% of a population are smokers,† then the small minority who are not smokers would appear, on the face of it, to be of some special type of constitution. It is not implausible that they should be on the average relatively longevous, and this implies that death rates generally in this segment of the population will be relatively low. After all, the small group of persons who successfully resist the incessantly applied blandishments and reflex conditioning of the cigarette advertisers are a hardy lot and, if they can withstand these assaults, they should have relatively little difficulty in fending off tuberculosis or even cancer! If it seems difficult to visualize how such a constitutional influnce can carry over to manifest itself as a graded increase of death rate with a graded increase of intensity of smoking, then we must remember that we are wandering in a wilderness of unknowns. I do not profess to be able to track out the implications of the constitutional theory or to defend it, but it cannot be disposed of merely by flat denial.‡

Another explanation that must be considered seriously is also referred to by Doll and Hill[5] in their recent report, when they said:

'If the association suggested by the upper part of the table§ were due merely to a bias

** In an important study by Caroline Bedell Thomas (J. Chronic Dis., March 1958, p. 198) in which findings in a group of medical students are correlated with history of vascular disease in their parents, is was found that:

'The incidence of parental hypertension and coronary disease was higher among subjects who were regular smokers than among subjects who were non-smokers or occasional smokers.'

This is direct evidence, so far as it goes, of hereditary constitutional basis for a relation between disease incidence and smoking.

* Cancer is a biologic, not a statistical, problem. Statistics can soundly play an ancillary role in its elucidation. But if biologists permit statisticians to become the arbiters of biologic questions, scientific disaster is inevitable.

† In the retrospective study of Doll and Hill,[7] less than 5% of the controls were non-smokers. In the prospective study[6] only 13% were non-smokers. In the prospective study of Hammond and Horn,[11] 17% were recorded as non-smokers (lifetime history).

‡ The rejection of the hypothesis of constitution by Doll and Hill, cited above, had reference to the association of smoking specifically with lung cancer. Doll and Hill may be more sympathetic to it in the light of the disclosure of the generalized associations.

§ Table XVII. It gives the standardized death rates for a summation of groups of causes of death that, it is said, have from time to time been regarded as possibly related to smoking. For this group of causes of death, taken together, the death rate increases monotonically with increase of smoking rate.

in our method of investigation, we would expect to see that bias operating to some extent in all, or nearly all, causes of death. It does not appear to do so.'

Although the wording of the quoted passage makes its exact meaning somewhat obscure, I take it to imply that a show of association of smoking with the death rates from all or nearly all causes of death would, in so far, be evidence that there may be a bias in the method of investigation. Does the finding in the data of Doll and Hill of association in all of the 5 categories of disease of their Table V, and the association with the more specific causes shown in the data of Hammond and Horn, satisfy the requirement of all or nearly all diseases?' So far as the data of Doll and Hill are concerned, the relatively small numbers of deaths reported render minute examination of specific causes of death not very profitable; however, by gathering together data from their Tables V, XIII and XVI, the death rates for the different classes of smokers may be examined in 15 categories of cause of death (Table 34). The death rate for the heavy smokers is higher than that for the non-smokers in 12 of the 15 categories, although in several instances the number of deaths, the difference of rates, or both, are small. It is notable that in the category containing cancer of other sites (other than respiratory, gastro-intestinal and prostate), there were 88 deaths (compared with 84 deaths from cancer of the lung), and this group shows a graded increase of death rate with increased amount of smoking, from a rate of 0.64 for non-smokers, to a rate of 1.02 for heavy smokers. There were 77 deaths by violence, almost as many as for lung cancer; while the death rates for violence do not increase monotonically with increasing intensity of smoking, the death rate is the highest for the heavy smokers (0.90), and the lowest for the non-smokers (0.42).

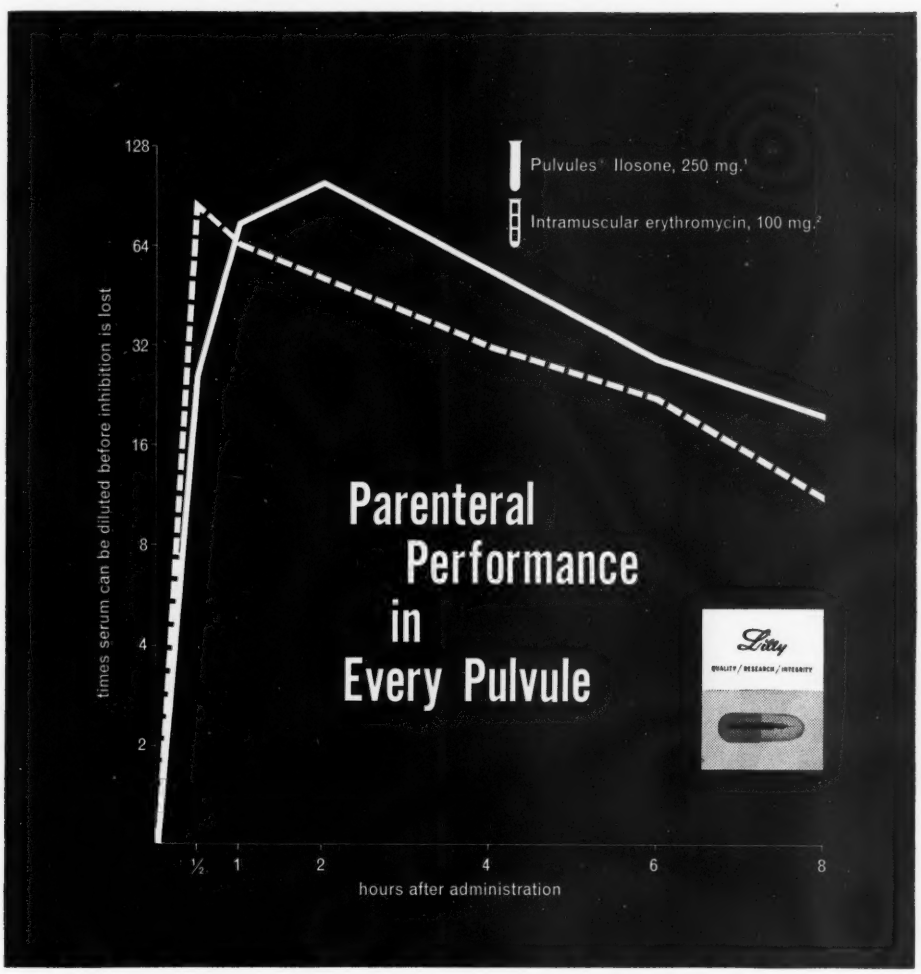
In the much more ample data of Hammond and Horn,[10] the categories represented in Fig. 1, in all of which association is exhibited, are fairly narrow. But even more to the point, their detailed data show association in many individual causes of death.[9] Indeed, in those data, it is more a matter of singling out the causes for which no association is evident, than of pointing out the causes for which there is association.§ Unless a case can be made out for assuming that there is bias in one rather than the other of the two prospective studies, it seems reasonable to consider them both together; when this is done, there can hardly be any doubt that association is shown for 'all or nearly all causes of death.' And, following Doll and Hill, this is indicative of the possible presence of bias.

I do not like the term 'bias,' since it may seem to imply conscious deception, though of

§ Recently, a number of independent studies have appeared reporting an association of smoking with diseases other than cancer of the lungs, such as tuberculosis,[13] cancer of the bladder,[12] prematurity of births and thyroidal disorders.[15]

TABLE 34: DEATH RATES FOR VARIOUS SMOKING CLASSES FOR INDIVIDUALIZED CATEGORIES OF DISEASE: REPORT OF DOLL AND HILL[5]

Category	*Deaths*	*Death Rate, Standardized, per* 1,000			
		Non-Smokers	*Men Smoking a Daily Average of*		
			1–14 *gm.*	15–24 *gm.*	25 + *gm.*
Cancer					
Lung	84	0·07	0·47	0·86	1·66
Upper respiratory and digestive tracts	13	0·00	0·13	0·09	0·21
Stomach	32	0·41	0·36	0·10	0·31
Colon and rectum	57	0·44	0·54	0·37	0·74
Prostate	30	0·55	0·26	0·22	0·34
Other sites	88	0·64	0·72	0·76	1·02
Respiratory diseases					
Pulmonary tuberculosis	19	0·00	0·16	0·18	0·29
Chronic bronchitis	42	0·12	0·29	0·39	0·72
Other respiratory diseases	65	0·69	0·55	0·54	0·40
Coronary thrombosis	508	4·22	4·64	4·60	5·99
Other cardiovascular diseases	279	2·23	2·15	2·47	2·25
Cerebral hemorrhage	227	2·01	1·94	1·86	2·33
Peptic ulcer	18	0·00	0·14	0·16	0·22
Violence	77	0·42	0·82	0·45	0·90
Other diseases	183	1·45	1·81	1·47	1·57



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1. Antibiotic Med. & Clin. Therapy, *5*:609, 1958.
2. Data from Antibiotics Annual, p. 269, 1954-1955.

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course Doll and Hill certainly did not mean to imply that. However, when an investigation set up to test the theory, suggested by evidence previously obtained, that smoking causes lung cancer, turns out to indicate that smoking causes or provokes a whole gamut of diseases, inevitably it raises the suspicion that something is amiss. It is as though, in investigating a drug that previously had been indicated to relieve the common cold, the drug was found not only to ameliorate coryza, but to cure pneumonia, cancer and many other diseases. A scientist would say: 'There must be something wrong with this method of investigation.'* It would be highly speculative, and invidious, to attempt to identify specifically what the character and mechanism of entry of such a bias are. However, it must be pointed out, that the observations constituting the two main variables under study, namely a history of smoking, and the cause of death, are subject to considerable and even extreme error,† and the samples are selected, possibly highly selected.‡ In the presence of a combination of such diversionary complications, we may expect 'almost anything' to happen.

If the observed statistical association between smoking and the death rate from many causes including cancer of the lung is not spurious, that is, if it is not a vagary of the data, and the 'constitution' explanation is considered unconvincing, another explanation that may be offered is that smoking increases the 'rate of living' (Pearl).[14] Actually I do not know of any independent evidence for such an effect of smoking. It is Pearl's concept, and the findings in the studies relating smoking to death rates, that suggested it. In their first report, Hammond and Horn[11] made the interesting observation that the general death rate among smokers, is similar to that among non-smokers of more advanced age, and this observation is consonant with the proposed theory. To be sure, nothing is known about the properties of tobacco smoke that would produce such an effect, or what specifically are the physicochemical alterations in the cell that constitute such a change. But neither is anything known about the physicochemical processes that constitute normal ageing. It is conceivable that smoking over a long period creates an altered internal environment for the body cells, which modifies the rate of those biologic processes that affect the ageing of tissues. But the most important consideration with respect to a theory is not whether it appears plausible, but whether it suggeste experiments, and what experiments are suggested. This theory does bring to mind experiments, but not those consisting of the application of products of tobacco smoke to tissues followed by observation to discern whether cancer develops. It suggests a programme of what might be called the experimental epidemiology of the

EXCESS DEATHS AMONG MEN WITH A HISTORY OF REGULAR CIGARETTE SMOKING

Coronary Artery Disease:	1,388	52·1%
Lung Cancer:	360	13·5%
Other Cancer:	359	13·5%
Other Heart & Circulation:	154	5·8%
Pulmonary (Excluding Cancer):	150	5·6%
Cerebral Vascular:	128	4·8%
Gastric & Duodenal Ulcers:	75	2·8%
Cirrhosis of the Liver:	40	1·5%
All Other:	11	0·4%
Total	2,665	

* However, a modern statistician, practised as he is in dialectics, may reply, 'The fact that the drug cures cancer does not disprove that it helps colds.'

† I have a study of this question under way.

‡ In the investigation of Doll and Hill, about 30% of the physicians to whom questionnaires on smoking were sent did not reply or sent a reply insufficiently complete to be utilized. In a case like the study of Hammond and Horn, the reference population is not definable. The amount of selection, therefore, cannot be estimated, and the problems of selection discussed by Brownlee[3] become more difficult of evaluation.

trophic ('chronic degenerative') diseases. I should take as a model the famous programme of experimental epidemiology of Greenwood, A. Bradford Hill, Topley and Wilson,[8] but the interest would be, not in infectious diseases and their mode of spread, but in diseases of no known specific cause, and their occurrence rates under different environmental conditions. Obviously, this is not the place to try to present the details of such an experimental programme. Its scope and general methodology can be gleaned by reference to the work just cited.

SUMMARY AND REMARKS

Firm opinions have been published to the effect that, on the basis of accumulated evidence, it is scientifically established beyond reasonable doubt, that smoking is an important cause of cancer of the lung. I am a member of a committee that has sponsored some of the most important of the published studies and, owing to this circumstance, have felt the responsibility to make a fairly careful study of this evidence. My own conclusions are quite different.

In the first place, virtually all the evidence is obtained from statistical studies in the ordinary connotation of the term 'statistical.' We are not dealing with the results of laboratory experiments, or even with placebo-controlled clinical trials. Nor is the conclusion based on a synthesis, by a 'chain of reasoning,' of relevant scientific knowledge from many different sources.* Such statistical evidence, for a question like the identification of a cause of a disease, at best, can be only presumptive. But even as statistical investigations, I do not find the published studies so sound or convincing as they apparently have widely been assumed to be. In the studies that have been called 'retrospective,' as well as in those called 'prospective,' I find questionable and even paradoxic elements.

In the present brief communication, I have referred to such a paradoxic element in two prominent prospective studies. These studies were projected as a check on the theory that smoking causes cancer of the lung, a theory derived from previous observations pointing to that specific conclusion. What the prospective studies actually revealed was an association of smoking, not specifically with lung cancer, but with a wide variety of diseases, including diseases that never have been conceived to have the same etiology as cancer. It is not logical to take such a set of results as confirming the theory that tobacco smoke contains carcinogenic substances which, by contact with the pulmonary tissues, initiate cancerous changes at the site of contact. Nor is it wise to look aside from positive findings that do not neatly fit the simple theory that initiated the investigation. Something more important may have been discovered than was first conceived. The results suggest that in data which have been obtained as these data have been collected there are factors which produce a statistical association between smoking and the death rate from disease generally. I have suggested for consideration 3 explanations.

1. The observed associations are 'spurious,' that is, they have no biologic significance, but are the result of the interplay of various subtle and complicated 'biases.' The definitive variables, namely a history of smoking and the cause of death, are, as observations, subject to considerable error, and the samples, not having been obtained (or obtainable) by scientific sampling methods, are 'selected.' In order to determine the effect of such errors and selection, it will be necessary to make independent investigations, and it may be difficult to plan and carry out such studies. At any rate, the possible effect of these factors is not determined scientifically by speculative reflections on what seems 'unreasonable,' or by declaration that this or that possible effect appears 'far-fetched.' What is required is *investigation.*

2. The observed associations have a constitutional basis. Persons who are non-smokers, or relatively light smokers, are the kind of people who are biologically self-protective, and biologically this is correlated with robustness in meeting mortal stress from disease generally.

3. Smoking increases the 'rate of living' (Pearl), and smokers at a given age are, biologically, at an age older than their chronologic age. As a result, smokers (in particular, heavy smokers) are subject to the death rates of non-smokers or relatively light smokers who are chronologically older. Diseases like cancer and heart disease, the death rates for which have a pronounced gradient with age, will be considerably more prominent in heavy smokers than in non-smokers or relatively light smokers of the same age. A particular significance of this theory is that it suggests a novel programme of experiments for verification—what

* As was the case for instance with the investigation of cholera by Snow, (Frost).[7a] In this connexion it is pertinent to quote the opinion of Stocks and Campbell.[15a] 'Certainty about the causation of lung cancer is unlikely to result from any single research, whether chemical, experimental, clinical, or statistical; most probably conclusions will have to be reached on the grounds of consistency between data and by piecing together evidence from diverse sources. . . .'

might be called the experimental epidemiology of non-infectious diseases. In this theory, it would not be expected that experiments with inhalation of tobacco smoke in animals specifically would produce lung cancer. The effect would be manifested in increased metabolic and vital activities, some of them possibly salutary, while at the same time death rates would be higher from diseases generally, especially the 'degenerative' or trophic diseases, which include cancer and cardiovascular diseases.

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PARAPHIMOSIS

R. A. FLEMING, *O.B.E.,* M.B., M.S., F.R.C.S., F.I.C.S.

Ministry of Health, Federation of the Rhodesias and Nyasaland

It is perhaps surprising that anything further can be said about this very ordinary minor surgical condition, but examination of any hospital records will speedily show that paraphimosis is responsible for far too many bed-day sojourns in hospital, and discussions with sufferers will reveal considerable mental and physical suffering.

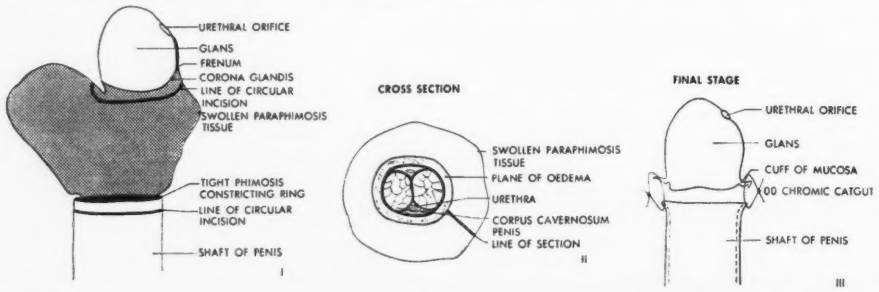
In this condition the prepuce cannot be pulled forwards after retraction behind the glans penis. It is very common in the African tribes who do not practise ritual circumcision and it may occur at any age, although it is chiefly a sequel of the first masturbation or sexual intercourse.

The cause is a pre-existing phimosis in the majority of cases (though some patients have an inflammatory condition in an otherwise normal prepuce).

The naked-eye appearances are those of a swollen, oedematous, retracted foreskin following pressure on the draining veins by the constriction band of the phimosis. This band ultimately becomes the site of pressure necrosis gangrene and local infection.

At birth the separation of the prepuce from the glans penis by tissue dehiscence is not complete and, if left untouched, the preputial orifice remains small. The prepuce can only with difficulty be pushed down over the glans and smegma material accumulates *in situ*.

Prophylactically, it would be wise to advise all midwives and doctors to include, in their examination of the new-born male child, manual full retraction of the prepuce back over the glans until the corona is well visualized and then to return the prepuce to its normal position. This manoeuvre completes the normal tissue dehiscence. The mother should be instructed to perform this simple action at bath time each day in cases where neonatal circumcision is not performed. In small babies erections are very common on the mildest stimulation, e.g. the cleaning and napkin changing, and the prepuce retracts and returns physiologically, so that phimosis is uncommon if the above routine is practised from the start.



The popular treatment of paraphimosis is manual reduction, in which the prepuce is restored to its normal position. This is possible only in the earliest cases. In the later cases, however, the 'dorsal slit' operation is performed whereby the constricting phimosis band is divided and the patient wanders desolately around with a swollen, dirty, potentially or actually septic mass of oedematous tissue at the end of his penis. This never really clears up and the ultimate circumcision is neither easy nor satisfactory.

The writer has, even in the pre-antibiosis era, always treated paraphimosis by the following immediate curative operation, and recommends it to practitioners faced with this problem.

The paraphimosis mass is retracted posteriorly so that the corona-preputial junction is put on the stretch. With a sharp knife this is divided circularly so that a short cuff of preputial tissue remains in continuity with the corona. The paraphimosis swelling is then retracted distally and another circular cut is made just proximal to the constricting band. A pair of curved-on-the-flat scissors is introduced to open up the plane between the penile shaft and the deep surface of the paraphimosis mass. This is easy because there is free oedema in this plane. The cuff of freed paraphimosis mass is divided in the axis of the penile shaft and is then pealed off. The mobile skin on the penile shaft is next approximated by interrupted 00 chromic catgut sutures to the cuff of prepuce around the corona glandis.

One hesitates to claim this procedure as a new operation because 'nothing in surgery is ever new'. However, the procedure described above was absolutely without complication in the writer's hands during the pre-antibiotic era, and the availability of these therapies makes the operation even safer today.

SUMMARY

The mental and physical morbidity of paraphimosis and the unnecessarily prolonged hospital stay of patients suffering from it are briefly described in this paper.

The popular 'dorsal slit' operation is condemned.

A prophylactic regime is suggested and a curative primary operation is described which speedily restores the organ to normal appearances and markedly shortens the patient's stay in hospital.

OPSOMMING

Die geestelike en fisiese morbiditeit van parafimose en die onnodig lank uitgerekte hospitaalverblyf van pasiënte wat daaraan ly, word kortliks in hierdie referaat beskryf.

Die gewilde 'dorsale gleuf'-operasie word veroordeel.

'n Profilaktiese regimen word aan die hand gedoen en 'n genesende primêre operasie word beskryf wat die normale voorkoms van die orgaan gou-gou herstel, en die pasiënt se verblyf in die hospitaal aanmerklik verkort.

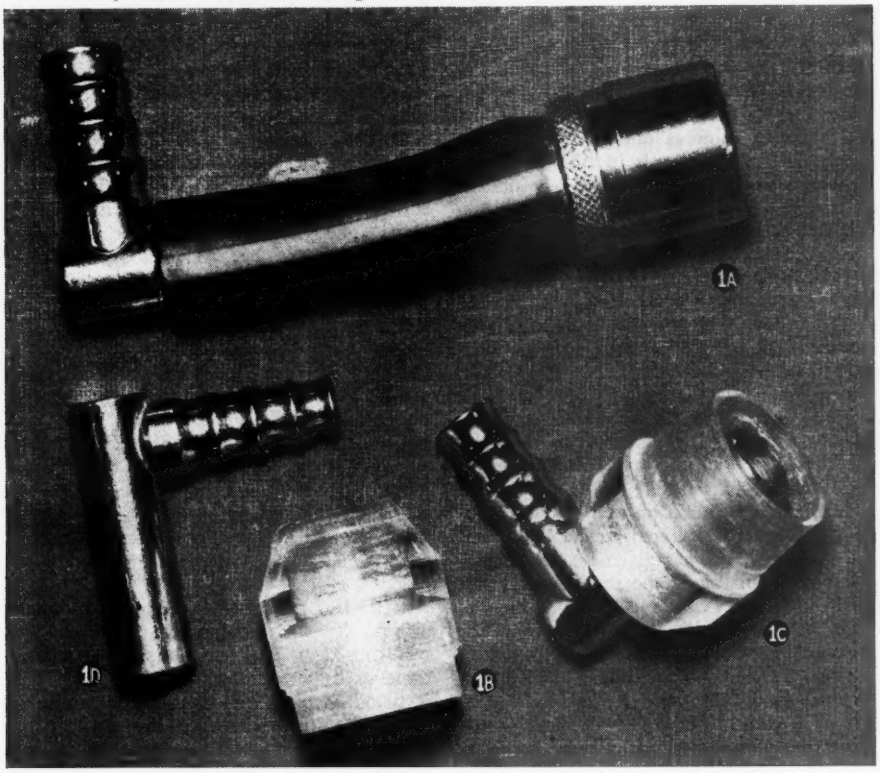
REDUCTION OF DEAD SPACE IN GENERAL ANAESTHESIA

AN IMPROVED INTRATRACHEAL NIPPLE

H. H. SAMSON, *M.B.E.*, M.R.C.S., L.R.C.P.
Johannesburg

Reduction of dead space is highly desirable in patients undergoing protracted operations, especially those who may not be able to compensate adequately, viz. young children, the aged and the seriously ill.

The physiological dead space, i.e. the volume of air from the bronchioles to the outlet at the mouth or nostril, can be reduced considerably by means of an intratracheal tube. However, currently used attachments (Fig. 1A) which connect the patient to the anaesthetic machine, create unphysiological dead space which is redundant even when the rubber tubing is considerably shortened.



Such devices still contain 6 c.c. or more of unnecessary dead space. This may well represent a fifth of the physiological dead space in a child, and is distributed as follows:

(*a*) In the metal connexion;

(*b*) Within the lumen of the rubber tubing;

(*c*) In the lumen of the nipple, especially the expanded portion.

The improved nipple (Fig. 1B) eliminates the dead space in (*b*) and (*c*). This is effected by inserting the metal connexion firmly into the nipple so that the end of the smooth limb is flush with the end of the nipple (Fig. 1C).

The nipple is made of Perspex, and is therefore light and slightly resilient. This provides a better fit.

The nipple is designed to fit the smooth limb of the various sizes of Rowbotham metal intratracheal connexions (Fig. 1D) and an M.I.E. or Boyle's point. It is durable, unbreakable and may be sterilized by boiling or autoclaving. It is not affected by the vapours of trichlorethylene or Fluothane.

I wish to express my appreciation to the Department of Medicine, University of the Witwatersrand, for the photograph.

MEDICO-LEGAL SECTION

ALLEGED NEGLIGENCE IN BLOOD TRANSFUSION

IN THE MATTER BETWEEN ELLIOTT AND DR. H. D.*

JUDGMENT

De Wet, J.: Plaintiff is a married woman aged about 32 years. On 29 November 1953 a curettage operation was performed on her in the early morning and her doctor prescribed a blood transfusion for the afternoon. That was arranged through the South African Blood Transfusion Service. According to the plaintiff's evidence the transfusion was administered by the defendant. Plaintiff was in the Colin Gordon Nursing Home and occupied a bed in a 4-bed ward. The transfusion commenced at 5.30 in the afternoon, the needle being inserted in a vein near the inside fold of her left elbow. Plaintiff says that defendant only stayed about 5 minutes and then left. She says that the nurse who was in attendance also left. Thereafter she says that she felt increasing discomfort and eventually severe pain which she described as 'excrutiating.' When the pain became unbearable she asked a patient in an adjoining bed to ring for the nurse who arrived after a few minutes and removed the needle. At that stage the blood in the bottle from which the transfusion was being administered had been reduced from 500 c.c. to about 200 c.c. Later the defendant came and the balance of the blood was administered in her right arm without ill effect as far as that arm was concerned. Plaintiff says that an area of about 6 inches of her left arm was swollen and discoloured. Hot formentations were applied but she still suffered severe pain and could not sleep, and was given a sedative pill. She left the Nursing Home the next day but the pain in her arm continued to be severe and the area of discoloration increased in size. She was given supersonic treatment, a form of heat treatment, by her doctor but this did not relieve the pain, and on 9 December she consulted a specialist, Mr. L., who administered an injection into nerve ganglia in her arm, which gave her some relief. She says that she suffered pain for a considerable time and still suffers some pain and discomfort in the arm.

Damages are claimed on the basis that the blood transfusion was administered in a negligent manner. Various acts of negligence are alleged in the declaration, but Mr. *Merber*, for the plaintiff, has confined his argument to one alleged act of negligence, namely the failure by defendant to put the plaintiff's arm in a splint when he administered the transfusion. In support of this allegation there is only the evidence of Dr. F., who was plaintiff's medical attendant, who say that except in exceptional circumstances a patient's arm should be put in a splint when a transfusion is administered to prevent flexion of the elbow joint which is liable to dislodge the needle which is inserted into her vein. Dr. F. is a practitioner of fairly limited experience in regard to blood transfusions. Medical men who gave evidence for the defendant disagreed with him. Dr. S., the Director of the South African Blood Transfusion Service, and two medical specialists, Dr. L. and Dr. W., all say that a patient is more likely to move and dislodge the needle if subjected to the discomfort of a splint than if simply told to keep the arm still. It is conceded by them that it cannot be expected that the patient will keep her arm absolutely still, but they say that a fair amount of movement can be indulged in without affecting the position of the needle which is always fixed in its position by means of Elastoplast. Dr. W., as a result of experiments undertaken by him, gave evidence to the effect that a flexion of the elbow joint of as much as 90 degrees from the horizontal would not dislodge the needle and would not interfere with the flow of blood.

It is clear from the evidence of the medical experts that the discoloration of plaintiff's arm was caused by a haematoma. According to these experts the most probable cause of this is blood seeping into the tissues surrounding the vein at the spot where the needle entered the vein; that is a seeping back either of the blood which is being administered or of a mixture of this blood and the patient's own blood. This is due to the pressure which is necessary in the administering of the transfusion. This they say is something which occurs fairly frequently when a blood transfusion is administered and cannot be avoided. It does appear from their evidence that the patient will experience pain when this happens and it seems to me that in those circumstances the

* Heard in the Supreme Court of South Africa (Witwatersrand Local Division), Johannesburg, June 1955, before the Hon. Mr. Justice de Wet.

transfusion should be discontinued and some other vein should be tried. It is possible that if plaintiff had been told this the blood transfusion may have been stopped at an earlier stage and some of the ill effects from which she suffered may have been avoided. But this failure is neither pleaded nor suggested as an act of negligence in the present case.

In my opinion it has not been established that failure to splint is an act of negligence. On the contrary, the evidence satisfies me that there was no negligence or departure from the recognized practice. Quite apart from this it seems unlikely that the needle in fact became dislodged and so injected blood into the tissues surrounding the vein. Plaintiff herself says that she did not move her arm as far as she is aware and it is unlikely that there was in fact a dislodgment of the needle. Plaintiff told Dr. W. that when the needle was extracted blood still flowed from it. According to this witness, this would have been unlikely if the needle had moved so as to inject blood into the surrounding tissues: in that event he would have expected an obstruction of the flow of blood and the formation of a blood-clot in the needle.

It appears from the evidence that the main cause of the pain and discomfort suffered by the plaintiff was the occurrence of a thrombosis in the vein itself, which the medical witnesses say is an unusual sequel of a blood transfusion, but one which cannot be avoided, and that this must be regarded as one of the natural hazards of the operation.

There will be judgment for the defendant with costs and qualifying fees are allowed for Dr. W.

NOTES AND NEWS : BERIGTE

Mr. Robin I. H. Welsh has commenced practice as a Specialist Surgeon at 303 Van Riebeeck Medical Buildings, Schoeman Street, Pretoria. (*Telephones*: *Residence*: 78-5676; *Rooms*: 3-2002).

* * *

Mr. Louis A. du Plessis, Thoracic Surgeon, wishes to notify his colleagues that he has changed his address to 302 Ingram's Corner, Twist Street, Hillbrow, Johannesburg. The telephone numbers remain unchanged: *Rooms*: 44-8837; *Residence*: 41-4090.

Dr. Louis A. du Plessis, Torakschirurg, wens kollegas in kennis te stel dat hy verander het van adres na Ingram's Corner 302, Twiststraat, Hillbrow, Johannesburg. Die telefoon nommers bly onverandered: *Spreekkamers*: 44-8837; *Woning*: 41-4090.

* * *

Dr. George I. Frank wishes to inform his colleagues that he has joined Dr. K. G. Irving and Dr. G. H. Robertson in practice as a Specialist Pathologist at 1007 Metro Centre, Bree Street, Johannesburg. (*Telephones*: *Rooms*: 23-8579; 23-8874; *Residence*: 44-2183).

* * *

THE SECOND INTERNATIONAL MEETING ON FORENSIC PATHOLOGY

The Second Meeting will be held in New York, N.Y., U.S.A., from 18 to 21 September 1960. The Conference will be associated with the dedication of the new building for the office of the Chief Medical Examiner of the City of New York.

Further information may be obtained from any of the following: Dr. Milton Helpern, 55 East End Avenue, New York 28, New York, U.S.A.; *or* Dr. Charles Larsen, Tacoma General Hospital, Tacoma 5, Washington, U.S.A.; *or* Dr. Francis E. Camps, 37 Welbeck Street, London, W.1, England.

Dr. L. J. A. Loewenthal has been made an Associate Editor of "Der Hautarzt" and a Corresponding Member of the Argentine Dermatological Society.

* * *

Mr. Allan Kark, B.Sc., M.B., Ch.B. (Rand.), F.R.C.S. (Eng.), has commenced practice as a Specialist Surgeon at 512 Sanlam Building, Smith Street, Durban. (*Telephones*: *Rooms*: 6-4626; 5-8217; *Residence*: 88-5519).

* * *

IMMEDIATE POSTOPERATIVE CARE

A NEW SQUIBB MEDICAL FILM

The film shows a wide variety of procedures, equipment, drugs, and special skills required to provide patients the same calibre of care during the immediate postoperative period that they received during the operation.

The film begins with scenes that apply to all patients: maintenance of a clear airway—observation of vital stages—various techniques of providing oxygen—control of pain—fluid therapy and blood replacement—the use of suction and special recovery room procedures and records.

Then portions of surgical procedures help the viewer understand the reason for the related recovery room procedures shown. For instance, having seen orthopaedic surgery, the viewer better understands the special problems of traction or suspension in the recovery room. In urology, special recovery room procedures relate to drainage catheters and irrigating fluids. Tonsillectomy patients require special positioning and *gentle* suctioning of the pharynx. The specific postoperative care of patients who have had ocular surgery centres on the prevention or control of motion. Special dressings that permit observation of circulation at the suture line are an interesting facet of postoperative care in plastic surgery.

Major intrathoracic surgery, including cardiovascular surgery, precedes on the screen, scenes related

to recovery room procedures. Hypothermia by means of refrigerated blankets, as well as by immersion in ice water, is shown to build understanding of the rewarming process that takes place in the recovery room. Special recovery room procedures following neurosurgery, gastro-intestinal surgery, and biliary tract surgery are also shown.

Available to the medical profession, free of charge, *Immediate Postoperative Care* is a 16 mm. sound film in colour; the running time is 30 minutes. The film was produced under the medical direction of Drs. Frank Glenn, M.D., John M. Beal, M.D., Joseph F. Artusio, Jr., M.D.

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THE CIBA FOUNDATION

A Panel consisting of Prof. C. H. Best (Toronto), Prof. E. J. Conway (Dublin), Dr. G. W. Corner (New York), Prof. A. Haddow (London), Prof. R. Nicolaysen (Oslo), Dr. A. S. Parkes (London), Prof. F. Verzár (Basle) and Prof. F. G. Young (Cambridge), with Prof. V. R. Khanolkar (Bombay) as corresponding member, has considered 91 papers from 22 countries for the *Ciba Foundation's Awards for 1959 for Research Relevant to the Problems of Ageing*, and the following Awards have been made (the names of leading authors only are given):

Prof. J. F. Danielli (London) "Some alternative states of amoeba, with special reference to life-span." £400;

Dr. R. Hinchcliffe (London) "Ageing of the special senses." £300;

Dr. G. C. Wood (Leeds) "Kinetic studies on the formation of fibrils from collagen solutions and their relation to development and ageing of collagen fibrils *in vivo*." £300;

Dr. J. Gross (Boston, Mass.) "(*a*) The influence of growth rate on neutral salt extracts of guinea pig dermis." "(*b*) Time-dependent solubility changes of collagen in vitro." £200;

Dr. G. L. Curran (Kansas City) "Effect of cholesterol synthesis inhibition in normocholesteremic young men." £100;

Dr. Emily M. Horrington (Baton Rouge, Louisiana) "Parabiosis of rats of different ages." £100;

Dr. Esther C. Jones (Birmingham, U.K.) "The effect of hypophysectomy on ageing of the ovary." £100;

Dr. O. Koldovsky (Prague) "Absorption of glucose and neutral fat from the gastro-intestinal tract during the post-natal development of the rat." £100;

Dr. M. R. Malinow (Buenos Aires) "The effect of estrogens on experimental atherosclerosis." £100;

Miss Margot Roach (London, Ontario) "The effect of age on the elasticity of human arteries." £100.

NEW PARKE, DAVIS DEVELOPMENT

Hitherto the manufacture of Parke, Davis products in South Africa has been carried out at Port Elizabeth while the offices of the South African Company were located in Johannesburg.

Parke, Davis Laboratories have recently completed building new offices and laboratory at Isando, on the main Jan Smuts Airport road from Johannesburg. The buildings, which were occupied at the beginning of October, comprise a frontal double storey building of modern design which houses the offices, a cafeteria, restrooms, first-aid rooms, reception etc. Behind this there is a fire-proof single storey laboratory in which is being carried out the manufacturing and testing processes necessary to produce 75% of the Parke, Davis products sold in the Union of South Africa and in the Federation, as well as increasingly higher quantities used in other Southern African countries.

Unique in pharmaceutical manufacturing in Africa is the synthesis of chloramphenicol and chloramphenicol palmitate in one section of the laboratory. This comprises the first stage in the manufacture of most items in the range of Chloromycetin products now available for prescribing. Equally unique in the Union, and also in Africa, will be the encapsulation of the range of medicaments available to the medical profession under the name of Kapseals.

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Westdene Products (Pty.) Ltd. have pleasure in announcing that the following new film has been added to their library: —

A Simple Method of Cataract Extraction Using Zonulysin (alpha-chymotrypsin). The film is made by Macqueen Films, Ltd. for S. Maw, Son & Sons, Ltd., England. 16 mm., sound, colour, running time 16½ minutes.

This workmanlike and straightforward film is accurate and descriptive. After a diagrammatic explanation of the function of alpha-chymotrypsin in dissolving-out the suspensory ligaments that bind the lens of the eye to the ciliary body, the film demonstrates how successful the theory is, in the hands of the expert eye surgeon, translated into practice. The delicate surgical manipulations are admirably shown, and the ease of removal of the lens when the enzyme has had its carefully timed effect is illustrated not once but several times. The method already claims over 100 successes, and the film should do much to widen the use of the technique.

Inquiries for loaning the film should be made to the Public Relations Officer, Westdene Products (Pty.) Ltd., P.O. Box 7710, Johannesburg.

REVIEWS OF BOOKS

BILHARZIASIS

International Work in Bilharziasis, 1948–1958; World Health Organization, 1959; 58 pages, 1s. 9d. Pretoria: Van Schaik's Bookstore (Pty.) Ltd., P.O. Box 724.

It is estimated that bilharziasis affects some 150,000,000 people throughout the world, in a broad belt extending from Japan through Iraq and Africa to South America. It thus ranks second in importance to malaria as a parasitic disease but, unlike malaria, its range is extending, in proportion as more land is brought under irrigation. (In a warm climate irrigation systems provide the snails, which are the intermediate hosts of the parasite, with an ideal habitat). The paradoxical situation thus arises that irrigation, which has been introduced on a wide scale with the intention of improving the lot of the agricultural community in underdeveloped countries,

may set in motion a trend leading to a deterioration of its health.

Control of bilharziasis is theoretically simple to achieve. In practice it is attended with the greatest difficulties because of the habits of the people, the hardiness of the snail vectors and the cost of the engineering works required to make the habitat uncongenial to the snails. Since its inception, WHO has paid much attention to this disease and has initiated and encouraged work on the many complex problems to which it gives rise.

This booklet (a reprint of a special number of the *Chronicle of the World Health Organization*) describes the problems and outlines the work that has been and is being done by WHO. It sketches the nature and extent of the problem of bilharziasis, discusses the role of molluscicides and engineering in its control, and illustrates the variety of special problems that arise by a full account of the WHO bilharziasis project at Leyte in the Philippines.

RUNNING COMMENTARIES ON THE ROUND

Clinical Involvements or The Old Firm: Being Running Commentaries on the Round. By H. Gardiner-Hill, M.D., F.R.C.P. (1958. Pp. 200. Illustrated. 37s. 6d. Postage 1s. 6d.). London and Durban: Butterworth & Co. (Publishers) Ltd.

This book has a lot to be said for it. It is amusing, instructive and easy to read. The little cartoons and sketches add to the interest and help to illustrate certain points.

The book is, in the author's words, a 'running commentary on ward rounds.' The title originates from the fact that when we approach a patient we ask ourselves: What is involved? What system? What level? What is the nature of the involvement?

Undergraduates and even post-graduates should learn a great deal of wisdom from the book. This type of clinical wisdom or judgment is all too rarely seen in print, and the book is a refreshing change from the usual textbook. However, it is by no means free of criticism. The author is very much occupied with ptosed organs to which he ascribes many symptoms. The reviewer personally feels that this was 'debunked' effectively many years ago; but it would appear that at St. Thomas's Hospital this entity is still a justifiable diagnosis.

The author also subscribes to the belief that if iodine is given for too long a period in the preoperative treatment of thyrotoxicosis, it loses its effectiveness (p. 43). This belief can surely be shared by very few modern endocrinologists. He also has an irritating habit of leaving a case uncompleted. On p. 41 he describes how a surgical colleague diagnosed a 'slow mesenteric thrombosis,' but does not tell us whether the diagnosis was confirmed in any way. Similarly on p. 45 he leaves one in the dark as to whether they eventually did an autopsy on a case with a nodule in the liver which was queried as a primary or a secondary malignancy.

He still talks about 'M & B' being used in treatment. This would confuse the present generation of students, who are more familiar with the term sulphonamide.

The use of the term 'praecordial pain' without defining exactly the situation of the pain, is misleading to students, and only perpetuates the old idea that left pectoral pain is usually angina, and disregards the most important substernal element.

Despite these criticisms, the book is well worth reading, and the student will acquire a great deal of what he learns on ward rounds and misses in the textbooks. The practitioner will like this book because it confirms his own thoughts, and helps to clarify his ideas.

NOTIFICATION OF COMMUNICABLE DISEASES

COMPARATIVE REVIEW OF HEALTH LEGISLATION

Offprint from Volume 9, No. 4, of the *International Digest of Health Legislation,* World Health Organization, Geneva, 51 pages, 3s. 6d. Pretoria: Van Schaik's Bookstore (Pty.) Ltd., P.O. Box 724.

Notification of cases of communicable diseases to the public health services is an essential prerequisite for the putting into operation of measures for the control of such diseases. Collaboration by medical practitioners is an indispensible factor, but it will be difficult to obtain that collaboration if practitioners find that the public health services have not acted upon their notifications or if the only tangible result of their efforts is the compilation of statistics. If, on the other hand, their patients benefit from notification and it does not represent too heavy an administrative burden, practitioners will willingly co-operate with the public health services.

These are some of the considerations to be borne in mind when establishing or amending regulations relating to the notification of communicable diseases.

At the present time most countries have such regulations. A recent study in the *International Digest of Health Legislation* reviews the legislation in about 50 countries and includes chapters on legislation; classes of notifiable communicable diseases; list of notifiable diseases; notification of carriers; when notification must be made; who must make notification; to whom notification must be made.

An *Appendix* contains examples of notification forms, and a list of bibliographical references completes the study.

MAJOR ENDOCRINE DISORDERS

Major Endocrine Disorders. By S. Leonard Simpson. With the Collaboration of A. Stuart Mason and G. I. M. Swyer. (1959. 3rd ed. Pp. 447 + Index. With 55 Figs. 50s.). London and Cape Town: Oxford University Press.

Simpson's *Major Endocrine Disorders* was one of the first authoritative accounts of clinical endocrinology. The two previous editions appeared in 1938 and 1948. The new edition is therefore timely, in view of the many major advances that have taken place in the last decade in our understanding of endocrine disorders.

The authors have avoided the temptation to bog down the reader in laboratory detail. Enough reference to modern laboratory investigations, including hormone assays, has been made, however, with the object of assisting the clinician and not as

a substitute ' for clinical judgment, which must constitute the basis of a sound medical practice.'

The chapter on *Diabetes Mellitus* contains a succinct account of the place of oral anti-diabetic drugs in the treatment of the mild diabetic.

The importance of chromosomal sex determination is recognized by the inclusion of a separate section dealing with this essential application to the diagnosis of intersex, e.g. male transvestists (where the genuine transvestist is genetically male) and cases of Klinefelter's syndrome (in which the sex chromatin patterns may be female).

The authors rightly stress the fact that an assumption has been made in interpreting the identification of the chromatin mass as the fused XX chromosomes.

The volume is attractively printed and illustrated with numerous extremely helpful clinical photographs.

It will prove invaluable to the undergraduate student and the general practitioner, as well as the physician specialist.

Each chapter is followed by a very full bibliography which provides an excellent guide to further more specialized reading in the case of each syndrome discussed.

ZOONOSES

Joint WHO: FAO Expert Committee on Zoonoses: Second Report. World Health Organization: Technical Report Series, 1959, No. 169; 83 pages. 3s. 6d. Pretoria: Van Schaik's Bookstore (Pty.) Ltd.

In August 1958, the Joint WHO: FAO Expert Committee on Zoonoses re-defined the term ' zoonoses ' as ' those diseases and infections which are naturally transmitted between vertebrate animals and Man '; more than 100 of these are now recognized. Domestic animal reservoirs of such diseases are a source of considerable danger for Man, and the Committee felt that, within national administrations, close collaboration in the development of animal disease control between the various agencies concerned (particularly the medical and veterinary services) was highly desirable.

The following major zoonoses were extensively discussed by the group (which represented 7 European countries, 2 American, one Asian and one Oceanic): salmonellosis, leptospirosis, animal tuberculosis, anthrax, psittacosis (ornithosis), Q fever, arthropod-borne viral encephalitides and hydatidosis. (Rabies, brucellosis and plague were not discussed at this meeting, as they have been dealt with by other expert committees of WHO and FAO). Taking each of these diseases in turn, the Committee considered its incidence, the role played by the different animals involved and the most suitable methods for control. Problems of diagnosis, the life-cycles of infecting organisms, links in the spread of infection to Man, the development of appropriate vaccines and the use of antibiotics in the treatment of several of these conditions, were the salient points in the discussion. Other important zoonoses were also more briefly considered.

The Committee noted the progress of the animal-serum survey for determining a possible relationship between animal and human influenza, initiated in some 25 countries, and advised its continuation and expansion. Recommendations were also made on the reporting of zoonoses, on methods of investigation of the ecology of wild-animal reservoirs, on the study and grouping of the ' orphan ' viruses and on the need for clarifying the natural history of specific disease agents, particularly with regard to the possible emergence of new zoonoses.

Annexed to the report are several useful notes on prescriptive and technical aspects of zoonoses control.

This publication brings to the attention of government authorities, and the medical and veterinary workers concerned, the new knowledge and field experience recently accumulated on the subject of this persistent threat to the public health and economy of many countries.

CORRESPONDENCE

STATISTICAL EVALUATION OF TREATMENT

To the Editor: I refer to Dr. Davidson's report on the use of Polaramine in 20 cases of allergy. I have no views on this drug—perhaps it is good; but if so, Dr. Davidson's study fails to prove this. His series is too small.

According to Fisher's formula for small numbers studied, results are significant if S is > 4 where $\frac{(a-b)^2}{a+b} = S$. In this formula ' a ' = the number of positive results and ' b ' = the negative results.

Dr. Davidson had 15 cases with an ' excellent ' response (' a ') and five in a lesser category (' b '). So that $\frac{10^2}{20} = 5$. This would appear to be significant. However, if an outside observer were to quibble over just *one* of the cases in the ' excellent ' group, and place this in the moderate group, then ' a ' would equal 14 and ' b ' would equal 6. In such circumstances Fisher's formula indicates $\frac{(14-6)^2}{20}$ which is 3.2 — a non-significant result. Everything therefore, hinges on the interpretation of one single case result. This is much too shaky for significance. Dr. Davidson may well be correct in his 'preliminary report', but he fails to prove his point. His series should be much larger; and not only that, in order to obviate the highly subjective nature of the investigation outlined, Dr. Davidson should use the double-blind technique so that neither he nor the patient knows whether Polaramine or an identical-looking dummy tablet is being administered.

S. Levin, M.B., B.Ch. (Rand), M.R.C.P. (Edin.), D.C.H. R.C.P. & S. (Eng.), Cert. Paed. (Can.).
67, Jenner Chambers,
Jeppe Street, Johannesburg.

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